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(54) Title: HYDRAULIC CEMENT BASED ON CALCIUM PHOSPHATE FOR SURGICAL USE

(57) Abstract: The hydraulic cement is based on calcium phosphate for surgical use. It comprises a first component comprising  $\alpha$ -tricalcium phosphate powder particles, a second component comprising calcium sulphate dihydrate, and a third component comprising water. Furthermore the hydraulic cement does not contain more calcium sulfate hemihydrate (CSH) than 10 % of the total amount of said calcium sulphate dihydrate (CSD). This cement has the advantage that it has not a very basic component such as TTCP, consists of a limited amount of components, sets fast, and is easy to mix.

### Hydraulic cement based on calcium phosphate for surgical use

This invention concerns a hydraulic cement based on calcium phosphate for surgical use according to the preamble of claim 1.

Calcium phosphate cements (CPC) are mixtures of one or several calcium phosphate powders that react with water to form a new calcium phosphate compound, generally an apatite. Through these chemical reactions, there is hardening of the aqueous paste. *In vivo* studies have shown that CPC are generally biocompatible, osteoconductive and somehow bioresorbable. Therefore, CPC have been the subject of a large and growing interest of the medical community. Several products have been introduced on the market. However, all of these products have some drawbacks

From the US-A 4 880 610 a mixture of an aqueous solution,  $\alpha$ -tricalcium phosphate ( $\alpha$ -TCP;  $\text{Ca}_3(\text{PO}_4)_2$ ), monocalcium phosphate monohydrate (MCPM;  $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ ), and calcium carbonate (CC;  $\text{CaCO}_3$ ) is known. Due to the presence of MCPM, the paste is initially acid. Therefore, dicalcium phosphate dihydrate (DCPD;  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ) crystals form during the initial seconds of the setting reaction, hence rendering the paste hard. These crystals have to be broken down to be able to keep a paste consistency and to be able to fill the bone defect with the cement paste. Hardening of the paste occurs in a second step via the formation of carbonated apatite. Due to the fact that the paste hardens in two steps, the cement cannot be mixed with a pestle and a spatula: it requires the use of a mixing machine providing large mechanical forces (to break DCPD crystals). For the surgeon, this is obviously a disadvantage.

From the US-A 5 338 356 a mixture of an aqueous solution,  $\alpha$ -TCP, tetracalcium phosphate (TTCP;  $\text{Ca}_4(\text{PO}_4)_2\text{O}$ ), dicalcium phosphate (DCP;  $\text{CaHPO}_4$ ) and hydroxyapatite (HA,  $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ ) is known. This paste sets via one single setting reaction to form an apatite. As a result, the mixing procedure is very simple. However, the presence of a very basic calcium phosphate (TTCP) decreases the bioresorbability of the set cement [4], which might be undesirable. Additionally, the cement formulation is rather complicated with its four different powder components.

From the US-A 4 518 430 a mixture of an aqueous solution, TTCP and DCP is known. As for the cement according to US-A 5 338 356, the use of a basic calcium phosphate (TTCP) reduces the bioresorbability of the cement. Moreover, the setting reaction is slow and must occur in the absence of blood flow.

From US-A 4 619 655 it is known to use plaster of Paris (= calcium sulphate hemihydrate, CSH;  $\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$ ) in combination with a calcium phosphate ceramic, such as a "calcium triphosphate". However, these mixtures do not contain CSD. Additionally, the calcium phosphate ceramic is not added as a powder but as particles. Particles larger than 20  $\mu\text{m}$  are not reactive enough. Therefore, the setting reaction that could result from the hydrolysis of  $\alpha$ -tricalcium phosphate particles would take a few hours which is far too long for a medical use.

From US-A 5 605 713 a mixture of "three to four calcium phosphates", in particular  $\alpha$ -TCP is known, but none of the mentioned calcium compounds is CSD.

From US-A 5 954 867 a method is known for „making a calcium phosphate cement which self-sets at ambient temperatures comprising combining a calcium phosphate salt which is substantially free of TTCP with an additional source of calcium and an aqueous solution adjusted with a base to maintain a pH of about 12.5 or above". Such a high basic pH-value is not desirable due to the adverse effect on the tissue cells which leads to a low compatibility of such a cement.

From US 6,206,957 a "biocement paste comprising (a) tricalcium phosphate (b) at least one further calcium phosphate-containing compound, (c) a cohesion promoter and (d) a setting accelerator, wherein components (a) and (b) form a cement powder, and components (c) and (d) are in an aqueous solution, wherein said cement powders...." is known. In this patent, not only one, but two calcium phosphate compounds were used, one being  $\alpha$ -TCP. However, no mention of CSD is made.

In the scientific literature, Nilsson et al. (Key Eng.Mater, vols. 218-220 (2202) pp 365-368) described the effects of mixing  $\alpha$ -TCP with CSH. But again, the use of CSD is not mentioned. Although some of the CSH is hydrolysed in CSD in the presence of water so that entanglement of CSD crystals can take place this reaction has to compete with a

second reaction taking place simultaneously and which is the hydrolysis of  $\alpha$ -TCP and entanglement of apatite crystals. The occurrence of two competing parallel reactions complicates the setting reaction and leads to interactions between the two competing setting reactions, hence leading to inadequate rheological properties of the cement paste. „Inadequate“ meaning that the paste requires more water to be a paste, which has a negative effect on the injectability of the cement paste and the final mechanical properties of the cement.

From WO02/05861 LIDGREN a cement composition is known which is based on an aqueous liquid, calcium sulfate hemihydrate (CSH) as a first reaction component, calcium phosphate as a second reaction component and an accelerator for the reaction of CSH with water. Therefore, as with the mixture of Nilsson, there are two simultaneous setting reactions taking place, namely the hydrolysis of CSH and of the calcium phosphate, which leads to inadequate rheological properties of the cement paste (bad injectability) and a hardened cement with poor mechanical properties.

It would be desirable therefore to provide a calcium phosphate cement which overcomes or alleviates in part or all of the above mentioned drawbacks

According to a broad aspect, the present invention solves the problem of providing a hydraulic cement based on calcium phosphate for surgical use which has not a very basic component such as TTCP, consists of a limited amount of components, sets fast, and is easy to mix.

The invention solves the posed problem with a cement that displays the features of claim 1 as well as with the use of such a cement that displays the features of claim 49.

CSH has a solubility roughly 10 times larger than that of CSD. Therefore, small amounts of CSH can have a very large impact on the cement. It is therefore very important to limit the CSH amount to a minimum, namely at least 10 times lower than the CSD amount. But it is preferable to lower this amount down to 1-2% and more preferably to 0%.

The cement according to the invention comprises a first component comprising  $\alpha$ -TCP powder particles, a second component comprising calcium sulphate dihydrate (CSD;  $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ) and a third component comprising water.  $\alpha$ -TCP acts as the setting component whereas CSD is simultaneously a lubricant and enables an adequate control of the Ca/P molar ratio.

CSD is a very biocompatible material. It is obtained by mixing CSH with water. CSD has a solubility in water close to 10mM (in calcium ions), i.e. much larger than the concentration of calcium ions in the body. As a result, CSD implanted in a human body disappears by passive dissolution. However, as CSD is much more soluble than the solubility of hydroxyapatite, and as the body contains a large amount of phosphate ions, hydroxyapatite can precipitate around CSD implants. Precipitation can be enhanced if hydroxyapatite crystals are already present around CSD crystals. In the compositions described in this patent,  $\alpha$ -TCP is transformed in an apatitic compound. CSD crystals can therefore be transformed into hydroxyapatite:



As a result,  $\alpha$ -TCP/CSD mixtures implanted *in vivo* becomes denser and stronger with the implantation time, until all CSD is dissolved. Additionally, the precipitation of hydroxyapatite provokes a slight acidification of the cement surroundings, which is positive to keep a high bioresorbability.

Solubility data shows that the equilibrium pH between CSD and hydroxyapatite is close to pH 4. Therefore, if the cement was placed in pure water, the equilibrium pH should tend towards this pH value. *In vivo*, the pH value in the cement pores will always tend to decrease to reach this low equilibrium pH value. However, the body fluids are buffered at a pH value close to 7,4. Therefore, there will always be a competition between the latter two reactions: (a) acidification of the cement to reach equilibrium and (b) buffering of the cement by body fluids.

The use of CSD has also the advantage to promote the flow properties of the cement paste. This improvement is characterised by the fact that the amount of mixing liquid can be reduced when the amount of CSD is increased.

In a preferred embodiment the powder particles of said first component have an average diameter inferior to 20  $\mu\text{m}$  and preferably inferior to 10  $\mu\text{m}$ . Typically the average particle diameter is chosen to be 1  $\mu\text{m}$ .

The setting time of the cement is an important property of the cement. If the setting time is too fast, the surgeon does not have time to use the cement before it is hard. If the setting time is too long, the surgeon must wait until he/she can close the wound. Therefore, an intermediate setting time is desirable. Values comprised between 1 and 20 minutes are in a good range. Preferable values are in the range of 2 to 15 minutes, in more details in the range of 5 to 12 minutes.

In a preferred embodiment at least one of the three cement components comprises a setting regulator; a setting regulator being either a setting accelerator or a setting retarder.

The setting time can be controlled by the particle size of the  $\alpha$ -TCP powder: the smaller the particle size, the faster the setting reaction. However, a decrease of the particle size can be difficult to achieve (especially for diameters below 1  $\mu\text{m}$ ). Therefore, other methods should be considered. A very efficient way to accelerate the setting time is to have large concentrations of phosphate ions in the mixing solution. This can happen via two ways: (i) a soluble phosphate salt is added as a powder in the cement formulation. Upon contact with the mixing solution, the phosphate salt dissolves, and hence accelerate the chemical reaction (LeChatelier principle). (ii) a soluble phosphate salt is pre-dissolved in the mixing liquid. Examples of soluble phosphate salts are  $\text{Na}_2\text{HPO}_4$ ,  $\text{NaH}_2\text{PO}_4$ ,  $\text{K}_2\text{HPO}_4$ ,  $\text{KH}_2\text{PO}_4$ ,  $\text{NH}_4\text{H}_2\text{PO}_4$ . Typical concentrations in the mixing liquid are in the range of 0,05 to 1,00 M. Another way to accelerate the setting reaction is to add nuclei for apatite crystal growth, as the nucleation step of the setting reaction is a limiting factor. Typically, apatite crystals can be used, preferably a calcium-deficient hydroxyapatite or hydroxyapatite powder. Small amounts (a few weight percents) are sufficient to drastically reduce the setting time.

When the setting time is too short, various setting additives can be added to increase the setting time. Typical examples are compounds which inhibits the nucleation and/or growth of apatite crystals. Common examples are pyrophosphate, citrate, or magnesium ions. One particularly interesting compound is calcium carbonate (CC;

$\text{CaCO}_3$ ). Carbonate ions are present in human bone. Additionally, carbonate ions are able to reduce the size of apatite crystals, probably via the inhibition of apatite crystal growth.

The Ca/P molar ratio of  $\alpha$ -TCP is 1.5. Any addition of CSD will lead to an increase of the global Ca/P molar ratio. Simultaneously, an addition of CSD will allow an additional precipitation of apatite, hence leading to larger mechanical properties, and lower porosity. It is well-known that the bioresorbability of calcium phosphate cements depends on the Ca/P molar ratio: an increase of the Ca/P molar ratio leads to a decrease of the bioresorption rate. Therefore, the resorbability of the cement can be controlled by the fraction of CSD used in the cement composition. For a low resorbability, a Ca/P molar ratio larger than 2 is ideal.

In recent years, the occurrence of osteoporotic fractures has dramatically increased. Considering the lack of adequate cure and the increasing number of elderly people, this trend is expected to continue. Osteoporotic fractures are often very difficult to repair, because the bone is very weak. It is therefore not possible to insert screws to hold osteosynthesis plates. A way to solve the problem is to inject a calcium phosphate cement into the osteoporotic bone to reinforce it. In order to prevent any extravasation of the cement into the tissues surrounding bone, it is very important to visualise the cement. The easiest way is to increase the radio-opacity of the cement, for example by means of contrasting agents. Metallic powders of tantalum, titanium or tungsten (among others) can be used. However, it might not be desirable to use such powders in partially bioresorbable cements. It is preferable to use liquid agents, such as iodine compounds. Examples are iopamidol, iohexol and iotrolan.

The injection of a CPC into an osteoporotic bone is only possible if the cement is well injectable. Often, CPC are not well injectable. The reason is a too large average particle size and a too low viscosity of the mixing liquid, leading to so-called filter pressing: when a pressure is applied on the cement paste (e.g. during cement injection), the liquid and solid phases are separated. The easiest way to solve the problem is to increase the viscosity of the mixing liquid, for example by adding small amounts of polysaccharides into the mixing liquid. Typical polymers that can be used are hyaluronic acid or salt, chondroitin sulphate, dermatan sulphate, heparan sulphate, heparin, dextran, alginate,

keratan sulphate, hydroxypropylmethyl cellulose, chitosan, xanthan gum, guar gum, carrageenan. The most interesting compounds are those already certified for medical applications, such as hyaluronate compounds. Typical concentrations are around 1% w/w.

The viscosity of the mixing liquid is (as seen above) important to prevent filter-pressing. The viscosity of the cement paste is also a very important factor. The cement viscosity should be high enough to prevent a too fast mix with body fluids, such as blood. A mix with body fluids could prevent cement setting and hence lead to complications. The paste viscosity is also very important to prevent cement extravasation during bone augmentation (injection of cement into bone): the larger the viscosity, the lower the risk of extravasation. Therefore, the cement viscosity should be larger than 1 Pa·s, preferably above 10 or even 100 Pa·s.

The viscosity of the cement paste depends obviously on the powder-to-liquid (P/L) ratio. An increase of the P/L ratio leads to a increase of the cement viscosity. If the P/L ratio is too high, the amount of mixing liquid is too low to fill up all the pores between the different solid particles, and hence to form a cement paste. The volume of mixing liquid (VL) should be in the range of:  $0.5 VT < VL < 10VT$  where VT is the powder volume of the cement paste. More typical values are in the range of  $1.0 VT < VL < 2.5VT$ . By volume is meant the real volume (and not the apparent volume), i.e. the weight divided by the density of the material.

CPC particles have the disadvantage that they do not have macropores, i.e. pores larger than  $50 - 100\mu\text{m}$  in diameter, in which blood vessels and bone cells can grow in. As a result, the bioresorption occurs layer-by-layer and not everywhere in the cement bulk. To prevent this, bioresorbable or biodegradable granules can be added to the cement paste, in particular CSD granules. Upon implantation, CSD granules will dissolve, hence leaving empty pores. Typically, these granules, e.g. CSD granules, should have an average size in the range of 100 to  $500\mu\text{m}$ .

A different way to create macropores in the cement structure is to incorporate gas bubbles in the cement paste. This incorporation can be promoted by adding a tensioactive agent. Tensioactive agents can also be used to incorporate a poorly water-

soluble contrasting agent into the cement paste, for example organic iodine compounds (see above). The tensio-active agent may be incorporated in one of said three components of the cement, preferably in the third component, and is preferably taken from the group of:

docusate sodium ( $C_{20}H_{37}NaO_7S$ ), sodium lauryl sulphate ( $C_{12}H_{25}NaO_4S$ ), stearic acid ( $C_{17}H_{35}COOH$ ), alkyldimethyl(phenylmethyl)ammonium chloride [CAS registry number 8001-54-5], benzethonium chloride ( $C_{27}H_{42}ClNO_2$ ), cetrimide ( $C_{17}H_{38}BrN$ ), glycerin monooleate ( $C_{21}H_{40}O_4$ ), polysorbate 20 ( $C_{58}H_{114}O_{26}$ ), polysorbate 21 ( $C_{26}H_{50}O_{10}$ ), polysorbate 40 ( $C_{62}H_{122}O_{26}$ ), polysorbate 60 ( $C_{64}H_{126}O_{26}$ ), polysorbate 61 ( $C_{32}H_{62}O_{10}$ ), polysorbate 65 ( $C_{100}H_{194}O_{28}$ ), polysorbate 80 ( $C_{64}H_{124}O_{26}$ ), polysorbate 81 ( $C_{34}H_{64}O_{11}$ ), polysorbate 85 ( $C_{100}H_{188}O_{28}$ ), polysorbate 120 ( $C_{64}H_{126}O_{26}$ ), polyvinyl alcohol ( $(C_2H_4O)_n$ ), sorbitan di-isostearate ( $C_{42}H_{80}O_7$ ), sorbitan dioleate ( $C_{42}H_{76}O_7$ ), sorbitan monoisostearate ( $C_{24}H_{46}O_6$ ), sorbitan monolaurate ( $C_{18}H_{34}O_6$ ), sorbitan monooleate ( $C_{24}H_{44}O_6$ ), sorbitan monopalmitate ( $C_{22}H_{42}O_6$ ), sorbitan monostearate ( $C_{24}H_{46}O_6$ ), sorbitan sesqui-isostearate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan sesquioleate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan sesquistearate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan tri-isostearate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan trioleate ( $C_{33}H_{63}O_{6.5}$ ), sorbitan tristearate ( $C_{33}H_{63}O_{6.5}$ ), glyceryl monooleate ( $C_{21}H_{40}O_4$ ), isopropyl myristate ( $C_{17}H_{34}O_2$ ), isopropyl palmitate ( $C_{19}H_{38}O_2$ ), lanolin [CAS registry number 8006-54-0], lanolin alcohols [CAS registry number 8027-33-6], hydrous lanolin [CAS registry number 8020-84-6], lecithin [CAS registry number 8002-43-5], medium chain triglycerides (no registry number), monoethanolamine ( $C_2H_7NO$ ), oleic acid ( $C_{17}H_{33}COOH$ ), polyethylene glycol monocetyl ether [CAS registry number 9004-95-9], polyethylene glycol monostearyl ether [CAS registry number 9005-00-9], polyethylene glycol monolauryl ether [CAS registry number 9002-92-0], polyethylene glycol monooleyl ether [CAS registry number 9004-98-2], polyethoxylated castor oil [CAS registry number 61791-12-6], polyoxyl 40 stearate ( $C_{98}H_{196}O_{42}$ ), polyoxyl 50 stearate ( $C_{118}H_{236}O_{52}$ ), triethanolamine ( $C_6H_{15}NO_3$ ), anionic emulsifying wax [CAS registry number 8014-38-8], nonionic emulsifying wax [CAS registry number 977069-99-0], and sodium dodecyl sulphate ( $NaC_{12}H_{25}SO_4$ ).

Quite often, bone defects are not due to a traumatic event, but to a disease, e.g. bone tumor, infection, etc... In these cases, it would be interesting to incorporate drugs, in particular pharmaceutically or physiologically active substances, preferably antibiotics,

anti-inflammatory drugs, anti-cancer drugs, peptides, and proteins such as growth factors.

The various features of novelty which characterise the invention are pointed out with particularity in the claims annexed to and forming part of this disclosure. For the better understanding of the invention, its operating advantages and specific objects attained by its use, reference should be made to the examples and descriptive matter in which are illustrated and described preferred embodiments of the invention.

#### Example 1

All the cement components were pre-heated at 37°C for one hour. 5g  $\alpha$ -TCP powder (specific surface area: 0,6 m<sup>2</sup>/g), 0,8g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 0,2g hydroxyapatite powder (SSA: 48 m<sup>2</sup>/g), and 2 ml 1,0% w/w hyaluronate solution (Mw = 1000 kDa) were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was 9,3 ± 1,1 min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was 22 ± 5 MPa.

#### Example 2

All the cement components were pre-heated at 37°C for one hour. 5g  $\alpha$ -TCP powder (SSA: 0,6 m<sup>2</sup>/g), 3,0g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 0,2g calcium-deficient hydroxyapatite powder (SSA: 27 m<sup>2</sup>/g), and 2,8 ml 1,0% w/w hyaluronate solution (Mw = 1000 kDa) were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was 12,0 ± 2,2 min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was 13 ± 3 MPa.

#### Example 3

All the cement components were pre-heated at 37°C for one hour. 5g  $\alpha$ -TCP powder (SSA: 0,6 m<sup>2</sup>/g), 1,0g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 2,0 g CSD granules (diameter 150 –250  $\mu$ m, 85% apparent density), 0,2g calcium-deficient hydroxyapatite powder (SSA:

27 m<sup>2</sup>/g), and 2,5 ml 1,0% w/w hyaluronate solution (Mw = 1000 kDa) were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was 10,0 ± 2,4 min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was 18 ± 4 MPa.

#### Example 4

All the cement components were pre-heated at 37°C for one hour. 5g α-TCP powder (SSA: 0,6 m<sup>2</sup>/g), 0,8g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 0,2 g calcium-deficient hydroxyapatite powder (SSA: 27 m<sup>2</sup>/g), and 2,5 ml of a solution containing 0,2 M Na<sub>2</sub>HPO<sub>4</sub> and 1,0% w/w hyaluronate (Mw = 1000 kDa) were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was 4,3 ± 0,7 min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was 28 ± 4 MPa.

#### Example 5

All the cement components were pre-heated at 37°C for one hour. 5g α-TCP powder (SSA: 0,6 m<sup>2</sup>/g), 0,8g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 2,4 ml of a solution containing 0,2M Na<sub>2</sub>HPO<sub>4</sub> and 1,0% w/w hyaluronate (Mw = 1000kDa), and 0,5 ml iopamidol solution were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was 6,5 ± 0,9 min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was 21 ± 5 MPa.

#### Example 6

All the cement components were pre-heated at 37°C for one hour. 5g α-TCP powder (SSA: 0,6 m<sup>2</sup>/g), 0,8g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 0,2g hydroxyapatite powder (SSA: 48 m<sup>2</sup>/g), and 2 ml of a solution containing 2,0% w/w hyaluronate (Mw = 1000 kDa) and 5% w/w gentamicin sulphate were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was 13,3 ± 1,6 min. The cement was placed in a

phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was  $19 \pm 4$  MPa.

#### Example 7

All the cement components were pre-heated at 37°C for one hour. 5g  $\alpha$ -TCP powder (SSA: 0,6 m<sup>2</sup>/g), 0,8g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 0,2 g calcium-deficient hydroxyapatite powder (SSA: 27 m<sup>2</sup>/g), 0,2g K<sub>2</sub>HPO<sub>4</sub> powder, and 2,8 ml of a solution containing 1,3 % w/w chondroitin sulphate (Mw = 1300 kDa) were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was  $5,9 \pm 0,7$  min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was  $25 \pm 5$  MPa.

#### Example 8

All the cement components were pre-heated at 37°C for one hour. 5g  $\alpha$ -TCP powder (SSA: 2,5 m<sup>2</sup>/g), 0,8g CSD powder (SSA: 0,3 m<sup>2</sup>/g), 0,2 g calcium-deficient hydroxyapatite powder (SSA: 27 m<sup>2</sup>/g), 0,2 g K<sub>2</sub>HPO<sub>4</sub> powder, and 2,8 ml of a solution containing 1,3 % w/w chondroitin sulphate (Mw = 1300 kDa) were mixed for 60 seconds in a beaker using a spatula. Afterwards, the cement paste was placed into a pre-heated mould and left to harden at 37°C. The setting time of the cement was  $5,9 \pm 0,7$  min. The cement was placed in a phosphate buffer solution for 24 hours and tested mechanically. The compressive strength of the cement was  $25 \pm 5$  MPa.

#### Example 9

x g  $\alpha$ -TCP (SSA = 2.4 m<sup>2</sup>/g) were mixed with 0.37g CSD (0.8 m<sup>2</sup>/g) and (4-0.37-x)g of calcium carbonate (CaCO<sub>3</sub>; 1.5 m<sup>2</sup>/g) where x varied between 3.20 and 3.63g. The powder was then mixed with 1.5-1.7 mL of a potassium phosphate solution (0.2 M KH<sub>2</sub>PO<sub>4</sub>) and the resulting paste was kneaded for 60 seconds. Afterwards, the paste was placed into a syringe whose tip had been previously cut off and its setting time was determined. The cement setting time increased gradually with an increase in CaCO<sub>3</sub> content. The x-ray diffraction analysis (XRD) of the cement after two days of incubation at 37C showed that the setting reaction was strongly slowed by the addition of CaCO<sub>3</sub>. However, the specific surface area of the cement was strongly increased (+50% with 5% CaCO<sub>3</sub>).

Example 10

The following pre-sterilized components, i.e. 7.26g a-TCP (SSA = 2.4 m<sup>2</sup>/g), 0.74g CSD (0.8 m<sup>2</sup>/g), 0.10g NaH<sub>2</sub>PO<sub>4</sub>, 2.0 mL of iopamidol (organic iodine solution) and 1.2 mL of a 4% sodium hyaluronate solution, were mixed together in a sterile and closed mixer. After 30 seconds of thorough mixing, the paste was injected from the mixer into two 2mL syringes. The paste present in the syringes was then injected into the osteoporotic vertebrae (BMD = -3.5) of a corpse. The x-ray analysis of the vertebra showed a very good radiographical contrast, as well as a perfect cement distribution (spherical distribution).

Example 11

9g a-TCP (SSA = 2.4 m<sup>2</sup>/g) were mixed with 0.9g CSD (0.8 m<sup>2</sup>/g), 2.1g of calcium carbonate powder (CaCO<sub>3</sub>; 1.5 m<sup>2</sup>/g; average diameter in number: 1.9 m), and 4.5 mL of a 0.1M MgSO<sub>4</sub>, 0.1M Na<sub>2</sub>HPO<sub>4</sub>, and 0.05 M Na<sub>2</sub>H<sub>2</sub>P<sub>2</sub>O<sub>7</sub> solution. After 2 minutes of mixing, the paste placed into a cylindrical form, and vibrated with a vibrator to eliminate air bubbles. The top of the form was then covered with a wet piece of cloth. Thirty minutes after setting (Setting time = 47 min +/- 5 min), the block was unmoulded and placed in 10 mL of phosphate buffer solution (pH 7.4, 0.15M) at 37C for 5 days. After that time, the block was dried at 60C for 3 days and then ground (with a mortar and a pestle) and sieved. The granules in the range of 0.125 mm to 2.8 mm were collected for further use in an in vivo application. All operations were performed in aseptic conditions with sterile components.

Example 12

9g a-TCP (SSA = 2.4 m<sup>2</sup>/g) were mixed with 0.9g CSD (0.8 m<sup>2</sup>/g), 2.1g of calcium carbonate powder (CaCO<sub>3</sub>; 1.5 m<sup>2</sup>/g; average diameter in number: 1.9 m), 4g of maltose crystals (0.2 mm in diameter), and 4.5 mL of a 0.1M MgSO<sub>4</sub>, 0.1M Na<sub>2</sub>HPO<sub>4</sub>, and 0.05 M Na<sub>2</sub>H<sub>2</sub>P<sub>2</sub>O<sub>7</sub> solution. After 2 minutes of mixing, the paste placed into a cylindrical form, and vibrated rapidly with a vibrator to eliminate air bubbles. The top of the form was then covered with a wet piece of cloth. Thirty minutes after setting (Setting time = 47 min +/- 5 min), the block was unmoulded and placed in 50 mL of phosphate buffer solution (pH 7.4, 0.15M) at 37C for 5 days. After that time, the block was dried at

60°C for 3 days for further use in an in vivo application. All operations were performed in aseptic conditions with sterile components.

**CLAIMS**

1. A hydraulic cement based on calcium phosphate for surgical use comprising
  - A) a first component comprising  $\alpha$ -tricalcium phosphate powder particles;
  - B) a second component comprising calcium sulphate dihydrate (CSD);
  - C) a third component comprising water,  
**characterized in that**
  - D) said hydraulic cement does not contain more calcium sulfate hemihydrate (CSH) than 10 % of the total amount of said calcium sulphate dihydrate (CSD).
2. Cement according to claim 1, characterized in that the amount of calcium sulfate hemihydrate (CSH) of the cement is lower than 5% of said calcium sulphate dihydrate (CSD).
3. Cement according to claim 2, characterized in that the amount of calcium sulfate hemihydrate (CSH) of the cement is lower than 2%, preferably lower than 1 % of said calcium sulphate dihydrate (CSD).
4. Cement according to claim 3, characterized in that essentially no calcium sulfate hemihydrate (CSH) is detectable in the cement.
5. Cement according to one of the claims 1 to 4, characterised in that the powder particles of said first component have an average diameter inferior to 20  $\mu\text{m}$  and preferably inferior to 10  $\mu\text{m}$ .
6. Cement according to one of the claims 1 to 5, characterised in that at least one of the three cement components comprises a setting regulator.
7. Cement according to one of the claims 1 to 6, characterised in that at least one of the cement components comprises a setting accelerator.
8. Cement according to claim 7, characterised in that the first or second component comprises a setting accelerator.

9. Cement according to claim 7 or 8, characterised in that the setting accelerator is an apatite powder.
10. Cement according to claim 7 or 8, characterised in that the setting accelerator is a calcium-deficient hydroxyapatite or hydroxyapatite powder.
11. Cement according to claim 7 or 8, characterised in that the setting accelerator is a water-soluble phosphate salt, preferably taken in the group of  $\text{Na}_2\text{HPO}_4$ ,  $\text{NaH}_2\text{PO}_4$ ,  $\text{K}_2\text{HPO}_4$ ,  $\text{KH}_2\text{PO}_4$  or  $\text{NH}_4\text{H}_2\text{PO}_4$ .
12. Cement according to one of the claims 1 to 11, characterised in that the third component comprises a setting accelerator.
13. Cement according to one of the claims 1 to 12, characterised in that the setting accelerator is a dissolved phosphate salt, preferably taken in the group of  $\text{Na}_2\text{HPO}_4$ ,  $\text{NaH}_2\text{PO}_4$ ,  $\text{K}_2\text{HPO}_4$ ,  $\text{KH}_2\text{PO}_4$  or  $\text{NH}_4\text{H}_2\text{PO}_4$ .
14. Cement according to one of the claims 1 to 13 characterised in that the setting regulator is a setting retarder.
15. Cement according to one of the claims 1 to claim 14, characterised in that the first or second component comprises a setting retarder.
16. Cement according to claim 14 or 15, characterised in that the setting retarder is taken from the group of citrate, pyrophosphate, carbonate or magnesium ions.
17. Cement according to one of the claims 1 to 16, characterised in that the setting time of the cement paste obtained by mixing said three components at 37°C is comprised between 1 and 20 minutes.
18. Cement according to one of the claims 1 to 17, characterised in that the setting time of the cement paste at 37°C is comprised between 2 and 15 minutes.

19. Cement according to claim 18, characterised in that the setting time of the cement paste at 37°C is comprised between 5 and 12 minutes.
20. Cement according to one of the claims 1 to 19, characterised in that the Ca/P molar ratio of the cement paste obtained by mixing said three components is larger than 1,5.
21. Cement according to claim 20, characterised in that the Ca/P molar ratio of the cement is equal to 1,667.
22. Cement according to claim 20, characterised in that the Ca/P molar ratio of the cement is larger than 1,667.
23. Cement according to claim 20, characterised in that the Ca/P molar ratio of the cement is equal or larger than 2,0.
24. Cement according to one of the claims 1 to 23, characterised in that one of the components contain a radiological contrasting agent.
25. Cement according to claim 24, characterised in that the radiological contrasting agent is a liquid compound, preferably an iodine compound.
26. Cement according to claim 25, characterised in that the radiological contrasting agent is an organic iodine compound, preferably iopamidol ( $C_{17}H_{22}I_3N_3O_8$ ), iohexol ( $C_{19}H_{26}I_3N_3O_9$ ), or iotrolan ( $C_{37}H_{48}I_6N_6O_{18}$ ).
27. Cement according to one of the claims 1 to 26, characterised in that one of said three components, preferably the third component, comprises an additive to control the cement rheology.
28. Cement according claim 27, characterised in that the third component comprises an additive to control the cement rheology.

29. Cement according to claim 27 or 28, characterised in that the additive used to control the cement rheology is taken from the group of polysaccharide derivatives, preferably hyaluronic acid or salt, chondroitin sulphate, dermatan sulphate, heparan sulphate, heparin, dextran, alginate, keratan sulphate, hydroxypropylmethyl cellulose, chitosan, xanthan gum, guar gum, or carrageenan.
30. Cement according to claim 27 or 28, characterised in that the additive used to control the cement rheology is hyaluronic acid and/or hyaluronic salt.
31. Cement according to one of the claims 27 to 30, characterised in that the concentration of the additive used to control the cement rheology is larger than 1 weight %, preferably superior to 2 weight %, of the third component.
32. Cement according to one of the claims 1 to 31, characterised in that the volume VL of the third component is in the range of  $0,5\text{ VT} \leq VL \leq 10,0\text{ VT}$  where VT is the total powder volume of the first and second component.
33. Cement according to claim 32, characterised in that the volume VL of the third component is in the range of  $1,0\text{ VT} \leq VL \leq 2,5\text{ VT}$  where VT is the total powder volume of the first and second component.
34. Cement according to one of the claims 1 to 33, characterised in that the first or second component of the cement may further comprise granules whose diameter are at least two times, preferably at least 10 times larger than the average diameter of said powder particles of said first component.
35. Cement according to claim 34, characterised in that the granules have an average diameter in the range of  $100\text{ }\mu\text{m}$  to  $500\text{ }\mu\text{m}$ .
36. Cement according to claim 35, characterised in that the granules have an average diameter in the range of  $200\text{ }\mu\text{m}$  to  $350\text{ }\mu\text{m}$ .

37. Cement according to one of the claims 34 to 36, characterised in that the granules are made of calcium phosphate, CSD, polymer or bioglass.
38. Cement according to one of the claims 1 to 37, characterised in that said first and second component is in the form of particles having an average diameter larger than 0,1  $\mu\text{m}$ .
39. Cement according to one of the claims 1 to 38, characterised in that one or more of said three components comprises pharmaceutically or physiologically active substances, preferably antibiotics, anti-inflammatory drugs, drugs against osteoporosis, anti-cancer drugs, peptides, and proteins such as growth factors.
40. Cement according to one of the claims 1 to 39, characterised in that the one of said three components, preferably the third component, comprises a tensio-active agent, preferably taken from the group of: docusate sodium ( $\text{C}_{20}\text{H}_{37}\text{NaO}_7\text{S}$ ), sodium lauryl sulphate ( $\text{C}_{12}\text{H}_{25}\text{NaO}_4\text{S}$ ), stearic acid ( $\text{C}_{17}\text{H}_{35}\text{COOH}$ ), alkyldimethyl(phenylmethyl)-ammonium chloride [CAS registry number 8001-54-5], benzethonium chloride ( $\text{C}_{27}\text{H}_{42}\text{ClNO}_2$ ), cetrimide ( $\text{C}_{17}\text{H}_{38}\text{BrN}$ ), glycerin monooleate ( $\text{C}_{21}\text{H}_{40}\text{O}_4$ ), polysorbate 20 ( $\text{C}_{58}\text{H}_{114}\text{O}_{26}$ ), polysorbate 21 ( $\text{C}_{26}\text{H}_{50}\text{O}_{10}$ ), polysorbate 40 ( $\text{C}_{62}\text{H}_{122}\text{O}_{26}$ ), polysorbate 60 ( $\text{C}_{64}\text{H}_{126}\text{O}_{26}$ ), polysorbate 61 ( $\text{C}_{32}\text{H}_{62}\text{O}_{10}$ ), polysorbate 65 ( $\text{C}_{100}\text{H}_{194}\text{O}_{28}$ ), polysorbate 80 ( $\text{C}_{64}\text{H}_{124}\text{O}_{26}$ ), polysorbate 81 ( $\text{C}_{34}\text{H}_{64}\text{O}_{11}$ ), polysorbate 85 ( $\text{C}_{100}\text{H}_{188}\text{O}_{28}$ ), polysorbate 120 ( $\text{C}_{64}\text{H}_{126}\text{O}_{26}$ ), polyvinyl alcohol ( $(\text{C}_2\text{H}_4\text{O})_n$ ), sorbitan di-isostearate ( $\text{C}_{42}\text{H}_{80}\text{O}_7$ ), sorbitan dioleate ( $\text{C}_{42}\text{H}_{76}\text{O}_7$ ), sorbitan monoisostearate ( $\text{C}_{24}\text{H}_{46}\text{O}_6$ ), sorbitan monolaurate ( $\text{C}_{18}\text{H}_{34}\text{O}_6$ ), sorbitan monooleate ( $\text{C}_{24}\text{H}_{44}\text{O}_6$ ), sorbitan monopalmitate ( $\text{C}_{22}\text{H}_{42}\text{O}_6$ ), sorbitan monostearate ( $\text{C}_{24}\text{H}_{46}\text{O}_6$ ), sorbitan sesqui-isostearate ( $\text{C}_{33}\text{H}_{63}\text{O}_{6.5}$ ), sorbitan sesquioleate ( $\text{C}_{33}\text{H}_{63}\text{O}_{6.5}$ ), sorbitan sesquistearate ( $\text{C}_{33}\text{H}_{63}\text{O}_{6.5}$ ), sorbitan tri-isostearate ( $\text{C}_{33}\text{H}_{63}\text{O}_{6.5}$ ), sorbitan trioleate ( $\text{C}_{33}\text{H}_{63}\text{O}_{6.5}$ ), sorbitan tristearate ( $\text{C}_{33}\text{H}_{63}\text{O}_{6.5}$ ), glyceryl monooleate ( $\text{C}_{21}\text{H}_{40}\text{O}_4$ ), isopropyl myristate ( $\text{C}_{17}\text{H}_{34}\text{O}_2$ ), isopropyl palmitate ( $\text{C}_{19}\text{H}_{38}\text{O}_2$ ), lanolin [CAS registry number 8006-54-0], lanolin alcohols [CAS registry number 8027-33-6], hydrous lanolin [CAS registry number 8020-84-6], lecithin [CAS registry number 8002-43-5], medium chain triglycerides (no registry number), monoethanolamine ( $\text{C}_2\text{H}_7\text{NO}$ ), oleic acid ( $\text{C}_{17}\text{H}_{33}\text{COOH}$ ), polyethylene glycol monocetyl ether [CAS registry number 9004-95-9], polyethylene glycol monostearyl ether [CAS registry number 9005-00-9],

polyethylene glycol monolauryl ether [CAS registry number 9002-92-0], polyethylene glycol monooleyl ether [CAS registry number 9004-98-2], polyethoxylated castor oil [CAS registry number 61791-12-6], polyoxyl 40 stearate ( $C_{98}H_{196}O_{42}$ ), polyoxyl 50 stearate ( $C_{118}H_{236}O_{52}$ ), triethanolamine ( $C_6H_{15}NO_3$ ), anionic emulsifying wax [CAS registry number 8014-38-8], nonionic emulsifying wax [CAS registry number 977069-99-0], and sodium dodecyl sulphate ( $NaC_{12}H_{25}SO_4$ ).

41. Cement according to one of the claims 1 to 40, characterised in that the specific surface area (SSA) of the powder particles of said first component is in the range of 0,05 to 10,00  $m^2/g$ .
42. Cement according to claim 41, characterised in that the specific surface area (SSA) of the first component is in the range of 1 to 2  $m^2/g$ .
43. Cement according to one of the claims 1 to 42, characterised in that the cement viscosity of the cement is larger than 1  $Pa\cdot s$  at a shear rate of  $400s^{-1}$ , one minute after the start of cement mixing.
44. Cement according to claim 43, characterised in that the cement viscosity of the cement is larger than 10  $Pa\cdot s$  at a shear rate of  $400s^{-1}$ , one minute after the start of cement mixing, preferably larger than 100  $Pa\cdot s$ .
45. Cement according to one of the claims 1 to 44, characterised in that it consists of a powder/liquid formulation to be mixed, whereby
  - a) the powder comprises said first and second component; and
  - b) the liquid comprises the third component.
46. Cement according to one of the claims 1 to 45, characterised in that it consists of the following parts:
  - c) a powder comprising said first and second component
  - d) a first viscous solution comprising said third component; and
  - e) a second solution comprising a contrasting agent.

47. Cement according to claim 46, characterised in that component a) additionally comprises water-soluble phosphate salts and component b) comprises a polymer, preferably sodium hyaluronate.
48. Cement according to one of the claims 1 to 47, characterised in that the setting time of the mixture of said three components is between 2 to 15 minutes, preferably between 5 and 12 minutes.
49. Use of the cement according to one of the claims 1 to 48, characterised in that the mixture of said three components is injected into an animal or human bone defect and set in vivo.
50. Method for producing a matrix of apatite as temporary bone replacement material, characterised in that said three components according to one of the claims 1 to 49 are mixed together and allowed to harden.
51. Method according to claim 50, characterised in that the first and second component are pre-mixed and the third component is added subsequently.
52. Temporary bone replacement material obtained by the method according to claim 50 or 51, characterised in that it comprises an apatite.
53. Temporary bone replacement material according to claim 52, characterised in that it comprises CSD embedded in said apatite matrix.
54. Granules or blocks obtained by hardening the cement according to one of the claims 1 to 48 for in vivo implants.

**AMENDED CLAIMS**

[Received by the International Bureau on 02 October 2003 (02.10.03):  
original claims 1,2,3 replaced by amended claims 1,2,3]

**CLAIMS**

1. A hydraulic cement based on calcium phosphate for surgical use comprising
  - A) a first component comprising  $\alpha$ -tricalcium phosphate powder particles;
  - B) a second component comprising calcium sulphate dihydrate (CSD);
  - C) a third component comprising water, whereby
  - D) said hydraulic cement does not contain more calcium sulfate hemihydrate (CSH) than 10 % of the total amount of said calcium sulphate dihydrate (CSD),  
**characterized in that**
  - E) the amount of calcium sulfate hemihydrate (CSH) of the cement is lower than 5% of said calcium sulphate dihydrate (CSD).
2. Cement according to claim 1, characterized in that the amount of calcium sulfate hemihydrate (CSH) of the cement is lower than 2 % of said calcium sulphate dihydrate (CSD).
3. Cement according to claim 2, characterized in that the amount of calcium sulfate hemihydrate (CSH) of the cement is lower than 1 % of said calcium sulphate dihydrate (CSD).
4. Cement according to claim 3, characterized in that essentially no calcium sulfate hemihydrate (CSH) is detectable in the cement.
5. Cement according to one of the claims 1 to 4, characterised in that the powder particles of said first component have an average diameter inferior to 20  $\mu\text{m}$  and preferably inferior to 10  $\mu\text{m}$ .
6. Cement according to one of the claims 1 to 5, characterised in that at least one of the three cement components comprises a setting regulator.

7. Cement according to one of the claims 1 to 6, characterised in that at least one of the cement components comprises a setting accelerator.
8. Cement according to claim 7, characterised in that the first or second component comprises a setting accelerator.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CH 03/00304

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L24/02 A61L27/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 05861 A (BONE SUPPORT AB; LIDGREN LARS (SE)) 24 January 2002 (2002-01-24) cited in the application page 5, line 29 -page 6, line 15 page 7, line 34 -page 8, line 21 claims 1-12 ---	1-54
A	WO 91 00252 A (UNITED STATES GYPSUM CO) 10 January 1991 (1991-01-10) claims 6-11 ---	1-54 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- \*&\* document member of the same patent family

Date of the actual completion of the International search

27 August 2003

Date of mailing of the International search report

04/09/2003

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CH 03/00304

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MIRTCHE A A ET AL: "CALCIUM PHOSPHATE CEMENTS: ACTION OF SETTING REGULATORS ON THE PROPERTIES OF THE -TRICALCIUM PHOSPHATE- MONOCALCIUM PHOSPHATE CEMENTS" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 10, no. 9, 1 November 1989 (1989-11-01), pages 634-638, XP000081742 ISSN: 0142-9612 abstract -----	1-54

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CH 03/00304

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210**

Continuation of Box I.1

Although claims 49-53 are directed to a method of surgical treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Rule 39.1(iv) PCT – Method for treatment of the human or animal body by surgery

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/CH 03/00304

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0205861	A 24-01-2002	SE	517168 C2	23-04-2002
		AU	7120901 A	30-01-2002
		EP	1301219 A1	16-04-2003
		SE	0002676 A	18-01-2002
		WO	0205861 A1	24-01-2002
WO 9100252	A 10-01-1991	AU	5950790 A	17-01-1991
		WO	9100252 A1	10-01-1991